Barb O'Bryen

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

127379

SEARCH REQUEST FORM

Requestor's Name: Rebecca Cook

Serial Number: 09/911195

Date: 7/15/04

Phone: Rem 4C70

Art Unit: 1614

Search Topic: Inv Kathleen Campbell

Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevent citations, authors, keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevent claim(s).

Please search method of using compound of claim 1 to prevent or treat ototoxicity.

Thanks
Rebecca

STAFF USE ONLY

Date completed: 7-16-04

Searcher: ADB

Terminal time: 50

Elapsed time: prep 30

CPU time:

Total time:

Number of Searches:

Number of Databases:

Search Site

___ STIC

___ CM-1

___ Pre-S

Type of Search

___ N.A. Sequence

___ A.A. Sequence

/ Structure

___ Bibliographic

Vendors

___ IG

404 STN

___ Dialog

___ APS

___ Geninfo

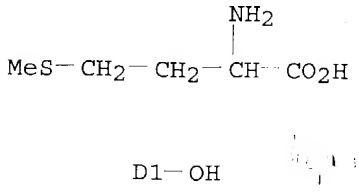
___ SDC

___ DARC/Questel

___ Other

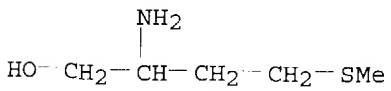
PTO-1590 (9-90)

RN 27459-44-5 REGISTRY
CN **Methionine, hydroxy- (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN DL-Methionine, hydroxy-
MF C5 H11 N O3 S
CI IDS



D1—OH

L6 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2004 ACS on STN
RN 502-83-0 REGISTRY
CN 1-Butanol, 2-amino-4-(methylthio)- (7CI, 8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN (1-(Hydroxymethyl)-3-(methylthio)propyl)amine
CN 2-Amino-4-(methylthio)-1-butanol
CN 2-Amino-4-methylthiobutanol
CN DL-Methioninol
CN **Methioninol**
CN NSC 67800
FS 3D CONCORD
DR 16720-80-2
MF C5 H13 N O S
CI COM
LC STN Files: ANABSTR, BEILSTEIN*, BIOSIS, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CSCHEM, MEDLINE, MSDS-OHS, SPECINFO, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); CMBI (Combinatorial study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

40 REFERENCES IN FILE CA (1907 TO DATE)
40 REFERENCES IN FILE CAPLUS (1907 TO DATE)
5 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

```
=> fil lreg;d ide
FILE 'LREGISTRY' ENTERED AT 16:01:37 ON 16 JUL 2004
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LREGISTRY IS A STATIC LEARNING FILE


L3    ANSWER 1 OF 2  COPYRIGHT 2004 ACS on STN
RN    29908-03-0  LREGISTRY
CN    Adenosine, 5'-[[(3S)-3-amino-3-carboxypropyl]methylsulfonio]-5'-deoxy-,
      inner salt (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN    Adenosine, 5'-[(3-amino-3-carboxypropyl)methylsulfonio]-5'-deoxy-,
      hydroxide, inner salt, (3S)-
CN    Adenosine, 5'-[(L-3-amino-3-carboxypropyl)methylsulfonio]-5'-deoxy-,
      hydroxide, inner salt (8CI)
CN    Methionine, S-adenosyl- (6CI)
OTHER NAMES:
CN    Active methionine
CN    Ademetionine
CN    AdoMet
CN    Donamet
CN    L-Methionine, S-adenosyl-
CN    L-S-Adenosylmethionine
CN    S Amet
CN    S-Adenosyl-L-methionine
CN    SAMe
FS    STEREOSEARCH
DR    23095-97-8, 2613-02-7, 86522-35-2, 86866-89-9, 5134-37-2, 28378-99-6
MF    C15 H22 N6 O5 S
CI    COM
LC    STN Files:   ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS,
        BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN,
        CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT,
        IFIUDB, IMSRESEARCH, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC,
        PIRA, PROMT, PS, RTECS*, TOXCENTER, USPAT2, USPATFULL
          (*File contains numerically searchable property data)
      Other Sources:   EINECS**
          (**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.
```

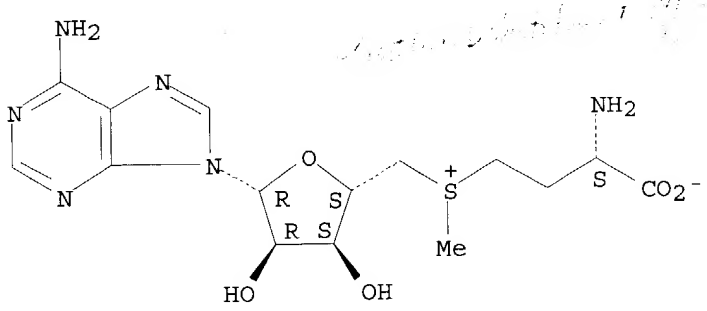


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=> d ide 1-2

L6    ANSWER 1 OF 2  REGISTRY  COPYRIGHT 2004 ACS on STN
```

FILE COVERS 1907 - 16 Jul 2004 VOL 141 ISS 4
FILE LAST UPDATED: 15 Jul 2004 (20040715/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE

```
L7              STR
L9          21755 SEA FILE=REGISTRY SSS FUL L7
L15          1509 SEA FILE=CAPLUS ABB=ON  (OTOTOX? OR OTOPROTECT?)/BI
L16           218 SEA FILE=CAPLUS ABB=ON  TOXICITY/CT(L)(OTO/OBI OR AUDITORY/OBI
                  OR EAR/OBI OR HEARING/OBI)
L17           658 SEA FILE=CAPLUS ABB=ON  EAR/CT(L)TOXICITY/OBI
L18          2004 SEA FILE=CAPLUS ABB=ON  EAR#/OBI(L)(DISEASE#/OBI OR DISORDER#/O
                  BI)
L19          1834 SEA FILE=CAPLUS ABB=ON  HEARING/CT
L20         23931 SEA FILE=CAPLUS ABB=ON  NOISE/OBI
L42           131 SEA FILE=CAPLUS ABB=ON  (ACOUSTIC OR SONIC OR SOUND)/BI(3A)(INJ
                  UR? OR TRAUMA? OR ACCIDENT?)/BI
L67             5 SEA FILE=CAPLUS ABB=ON  L9 AND (L20 OR L42) AND (L15 OR L16 OR
                  L17 OR L18 OR L19)
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=> fil embase; d que nos l38; d que nos l39

FILE 'EMBASE' ENTERED AT 16:46:46 ON 16 JUL 2004

FILE COVERS 1974 TO 15 Jul 2004 (20040715/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
L7              STR
L9          21755 SEA FILE=REGISTRY SSS FUL L7
L11            37 SEA FILE=REGISTRY ABB=ON  L9 AND EMBASE/LC
L23         22129 SEA FILE=EMBASE ABB=ON  L11
L27          1561 SEA FILE=EMBASE ABB=ON  NOISE INJURY/CT
L38             2 SEA FILE=EMBASE ABB=ON  L23 AND L27
```

```
L7              STR
L9          21755 SEA FILE=REGISTRY SSS FUL L7
L11            37 SEA FILE=REGISTRY ABB=ON  L9 AND EMBASE/LC
```

```
=> fil reg; d stat que l9
FILE 'REGISTRY' ENTERED AT 16:46:45 ON 16 JUL 2004
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   15 JUL 2004  HIGHEST RN 710826-40-7
DICTIONARY FILE UPDATES:  15 JUL 2004  HIGHEST RN 710826-40-7

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

L7                STR
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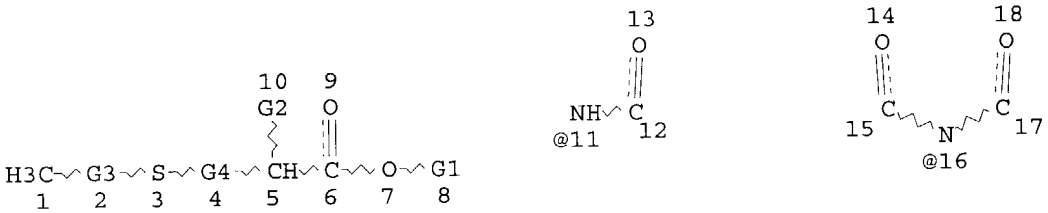


```
VAR G1=H/C
VAR G2=NH2/11/16
REP G3=(0-3) CH2
REP G4=(1-3) CH2
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  18

STEREO ATTRIBUTES: NONE
L9        21755 SEA FILE=REGISTRY SSS FUL L7

100.0% PROCESSED 343587 ITERATIONS                 21755 ANSWERS
SEARCH TIME: 00.00.04


=> fil capl; d que nos 167

FILE 'CAPLUS' ENTERED AT 16:46:46 ON 16 JUL 2004
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```

```
L23       22129 SEA FILE=EMBASE ABB=ON  L11
L25        5962 SEA FILE=EMBASE ABB=ON  OTOTOXICITY/CT
L26       21241 SEA FILE=EMBASE ABB=ON  NOISE+NT/CT
L28        8176 SEA FILE=EMBASE ABB=ON  HEARING LOSS/CT
L39           2 SEA FILE=EMBASE ABB=ON  L23 AND (L25 OR L28) AND L26


=> s l38 or l39

L76           4 L38 OR L39

=> fil medl; d que nos l47

FILE 'MEDLINE' ENTERED AT 16:46:48 ON 16 JUL 2004

 FILE LAST UPDATED: 15 JUL 2004 (20040715/UP). FILE COVERS 1951 TO DATE.

 On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD
 for details. OLDMEDLINE now back to 1951.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


L7              STR
L9        21755 SEA FILE=REGISTRY SSS FUL L7
L10          74 SEA FILE=REGISTRY ABB=ON  L9 AND MEDLINE/LC
L44       29203 SEA FILE=MEDLINE ABB=ON  L10
L45       11094 SEA FILE=MEDLINE ABB=ON  NOISE+NT/CT
L46        4197 SEA FILE=MEDLINE ABB=ON  HEARING LOSS, NOISE-INDUCED+NT/CT
L47           6 SEA FILE=MEDLINE ABB=ON  L44 AND (L45 OR L46)


=> fil drugu; d que nos l56

FILE 'DRUGU' ENTERED AT 16:46:49 ON 16 JUL 2004
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FILE LAST UPDATED: 15 JUL 2004        <20040715/UP>
>>>  DERWENT DRUG FILE (SUBSCRIBER)  <<<

>>>  FILE COVERS 1983 TO DATE  <<<
>>>  THESAURUS AVAILABLE IN /CT  <<<

>>>  A RECENT REVIEW OF PSYCHIATRIC DISEASE KEYWORDS USED
     IN DERWENT DRUG FILE HAS PROMPTED A REVISION BASED
     ON STANDARD TERMS USED IN DSM-IV (DIAGNOSTIC AND
     STATISTICAL MANUAL OF MENTAL DISORDERS - FOURTH
     EDITION).
     FOR FURTHER DETAILS:
http://thomsonderwent.com/derwenthome/support/userguides/lit_guide


L7              STR
L9        21755 SEA FILE=REGISTRY SSS FUL L7
L12          19 SEA FILE=REGISTRY ABB=ON  L9 AND DRUGU/LC
```

```
L48          475 SEA FILE=DRUGU ABB=ON  L12
L49         1678 SEA FILE=DRUGU ABB=ON  OTOTOX? OR OTOPROTECT?
L50         1426 SEA FILE=DRUGU ABB=ON  NOISE
L51         1949 SEA FILE=DRUGU ABB=ON  HEARING
L53           15 SEA FILE=DRUGU ABB=ON  (ACOUSTIC OR SONIC OR SOUND)(3A)(INJUR?
                 OR TRAUMA? OR ACCIDENT?)
L55           28 SEA FILE=DRUGU ABB=ON  (EAR#)(3A)(INJUR? OR TRAUMA? OR
                 ACCIDENT?)
L56            0 SEA FILE=DRUGU ABB=ON  L48 AND (L49 OR L51 OR L55) AND (L50 OR
                 L53)


=> fil biosis; d que nos 166

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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 15 July 2004 (20040715/ED)

FILE RELOADED: 19 October 2003.


L7                STR
L9           21755 SEA FILE=REGISTRY SSS FUL L7
L13            132 SEA FILE=REGISTRY ABB=ON  L9 AND BIOSIS/LC
L58          28298 SEA FILE=BIOSIS ABB=ON  L13
L59           2288 SEA FILE=BIOSIS ABB=ON  OTOTOX? OR OTOPROTECT?
L60          31396 SEA FILE=BIOSIS ABB=ON  NOISE
L61            564 SEA FILE=BIOSIS ABB=ON  (ACOUSTIC OR SONIC OR SOUND)(5A)(INJUR?
                  OR TRAUMA? OR ACCIDENT?)
L62          28497 SEA FILE=BIOSIS ABB=ON  HEARING
L63            127 SEA FILE=BIOSIS ABB=ON  AUDITOR?(3A)TOXIC?
L64            796 SEA FILE=BIOSIS ABB=ON  (EAR#)(3A)(INJUR? OR TRAUMA? OR
                 ACCIDENT?)
L66              1 SEA FILE=BIOSIS ABB=ON  L58 AND (L59 OR L63 OR L62 OR L64) AND
                 (L60 OR L61)


=> fil PASCAL, JICST-EPLUS, ESBIOBASE, LIFESCI, CONFSCI, DISSABS, WPIDS, scisearch

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=> d que nos l74

L68        67192 SEA METHIONINE
L69       533312 SEA NOISE OR (ACOUSTIC OR SONIC OR SOUND)(5A)(INJUR? OR
                 TRAUMA? OR ACCIDENT?)
L70         5452 SEA OTOTOX? OR OTOPROTECT?
L71        97222 SEA HEARING
L72          196 SEA AUDITOR?(3A) TOXIC?
L73          851 SEA (EAR#)(3A)(INJUR? OR TRAUMA? OR ACCIDENT?)
L74            9 SEA L68 AND L69 AND (L70 OR L71 OR L72 OR L73)


=> dup rem l67,l47,l66,l76,l74
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PROCESSING COMPLETED FOR L67
PROCESSING COMPLETED FOR L47
PROCESSING COMPLETED FOR L66
PROCESSING COMPLETED FOR L76
PROCESSING COMPLETED FOR L74
L77           18 DUP REM L67 L47 L66 L76 L74 (7 DUPLICATES REMOVED)
                 ANSWERS '1-5' FROM FILE CAPLUS
                 ANSWERS '6-10' FROM FILE MEDLINE
                 ANSWERS '11-14' FROM FILE EMBASE
                 ANSWER '15' FROM FILE CONFSCI
                 ANSWER '16' FROM FILE WPIDS
                 ANSWERS '17-18' FROM FILE SCISEARCH
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=> d ibib ed abs hitstr 1-5; d iall 6-18

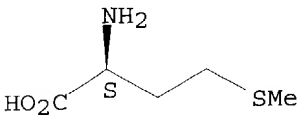
L77 ANSWER 1 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2003:796308 CAPLUS
DOCUMENT NUMBER: 139:286365
TITLE: Methods for preventing and treating loss of balance function due to oxidative stress
INVENTOR(S): Kopke, Richard D.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 16 pp., Cont.-in-part of U.S. Pat. Appl. 2001 7,871.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003191064	A1	20031009	US 2003-401682	20030331
US 2001007871	A1	20010712	US 2001-766625	20010123
US 6649621	B2	20031118		

PRIORITY APPLN. INFO.: US 2001-766625 A2 20010123
US 1997-69761P P 19971216
US 1998-126707 A2 19980731

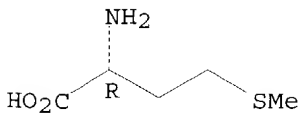
ED Entered STN: 10 Oct 2003
AB The present invention provides methods for preventing and treating loss of, or impairments to, the sense of balance. Specifically, the invention provides methods for preserving the sensory hair cells and neurons of the inner ear vestibular app. by preventing or reducing the damaging effects of oxidative stress by administering an effective amt. of the following therapeutic agents: antioxidants; compds. utilized by inner ear cells for synthesis of glutathione; antioxidant enzyme inducers; trophic factors; mitochondrial biogenesis factors; and combinations thereof. Acetyl-L-carnitine, D-methionine, and .alpha.-lipoic acid prevented loss of inner ear function and hair cell loss in chinchillas stressed with loud noise.
IT **63-68-3**, L-Methionine, biological studies **348-67-4**, D-Methionine
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(used in inner ear cells for synthesis of glutathione; antioxidants and other agents for preventing and treating loss of balance function due to oxidative stress)
RN 63-68-3 CAPLUS
CN L-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 348-67-4 CAPLUS
CN D-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

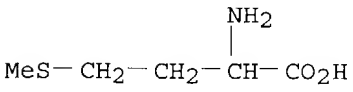


L77 ANSWER 2 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2002:123601 CAPLUS
DOCUMENT NUMBER: 136:145293
TITLE: Therapeutic use of D-methionine to reduce the toxicity of **noise**
INVENTOR(S): Campbell, Kathleen C. M.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 21 pp., Cont.-in-part of U.S. 6,265,386.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002019443	A1	20020214	US 2001-911195	20010723
US 6187817	B1	20010213	US 1997-942845	19971002
US 6265386	B1	20010724	US 1998-57065	19980408
US 2004110719	A1	20040610	US 2003-694448	20031027
US 2004127568	A1	20040701	US 2003-694432	20031027

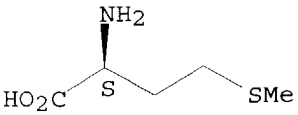
PRIORITY APPLN. INFO.: US 1997-942845 A2 19971002
US 1998-57065 A2 19980408
US 1996-27750P P 19961003
US 2001-911195 A1 20010723

OTHER SOURCE(S): MARPAT 136:145293
ED Entered STN: 15 Feb 2002
AB Methods of preventing or reducing hearing or balance loss and damage to ear cells in patients who have been exposed to toxic levels of noise are provided. These methods comprise administering an effective amt. of a methionine protective agent, such as D-methionine, prior to, simultaneously with, or subsequently to exposure to noise. Combinations of these time periods can also be employed.
IT **59-51-8**, Methionine **63-68-3**, L-Methionine, biological studies **348-67-4**, D-Methionine **1319-79-5** **13073-35-3**, Ethionine **29908-03-0**, S-Adenosyl-L-methionine
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic use of D-methionine to reduce **noise** toxicity)
RN 59-51-8 CAPLUS
CN Methionine (9CI) (CA INDEX NAME)



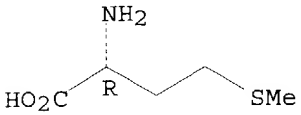
RN 63-68-3 CAPLUS
CN L-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry.

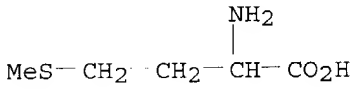


RN 348-67-4 CAPLUS
CN D-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



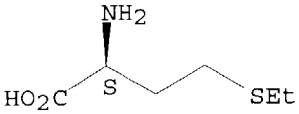
RN 1319-79-5 CAPLUS
CN L-Methionine, hydroxy- (9CI) (CA INDEX NAME)



D1—OH

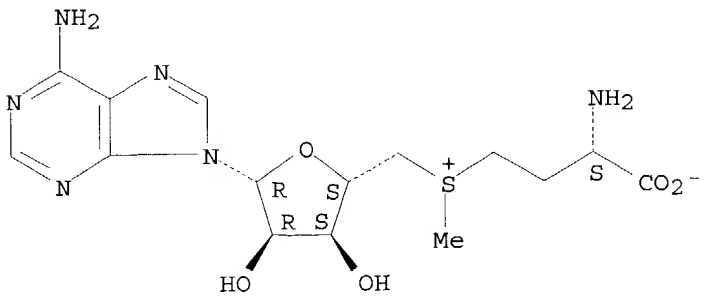
RN 13073-35-3 CAPLUS
CN L-Homocysteine, S-ethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 29908-03-0 CAPLUS
CN Adenosine, 5'-[[(3S)-3-amino-3-carboxypropyl]methylsulfonio]-5'-deoxy-, inner salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L77 ANSWER 3 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3

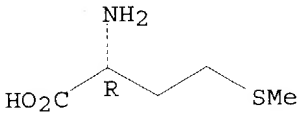
ACCESSION NUMBER: 2002:738271 CAPLUS
DOCUMENT NUMBER: 138:396100
TITLE: Enhancing Intrinsic Cochlear Stress Defenses to Reduce **Noise**-Induced Hearing Loss
AUTHOR(S): Kopke, Richard D.; Coleman, John K. M.; Liu, Jianzhong; Campbell, Kathleen C. M.; Riffenburgh, Robert H.
CORPORATE SOURCE: Dep. Defense Spatial Orientation Center, Naval Medical Center San Diego, San Diego, CA, USA
SOURCE: Laryngoscope (2002), 112(9), 1515-1532
CODEN: LARYA8; ISSN: 0023-852X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 30 Sep 2002
AB Oxidative stress plays a substantial role in the genesis of noise-induced cochlear injury that causes permanent hearing loss. We present the results of three different approaches to enhance intrinsic cochlear defense mechanisms against oxidative stress. This article explores, through the following set of hypotheses, some of the postulated causes of noise-induced cochlear oxidative stress (NICOS) and how noise-induced cochlear damage may be reduced pharmacol. (1) NICOS is in part related to defects in mitochondrial bioenergetics and biogenesis. Therefore, NICOS can be reduced by acetyl-L-carnitine (ALCAR), an endogenous mitochondrial membrane compd. that helps maintain mitochondrial bioenergetics and biogenesis in the face of oxidative stress. (2) A contributing factor in NICOS injury is glutamate excitotoxicity, which can be reduced by antagonizing the action of cochlear N-methyl-D-aspartate (NMDA) receptors using carbamathione, which acts as a glutamate antagonist. (3) Noise-induced hearing loss (NIHL) may be characterized as a cochlear-reduced glutathione (GSH) deficiency state; therefore, strategies to enhance cochlear GSH levels may reduce noise-induced cochlear injury. The objective of this study was to document the redn. in noise-induced hearing and hair cell loss, following application of ALCAR, carbamathione, and a GSH repletion drug D-methionine (MET), to a model of noise-induced hearing loss. This was a prospective, blinded observer study using the above-listed agents as modulators of the noise-induced cochlear injury response in the species Chinchilla laniger. Adult C. laniger had baseline-hearing thresholds detd. by auditory brainstem response (ABR) recording. The animals then received injections of saline or saline plus active exptl. compd. starting before and continuing after a 6-h 105 dB SPL continuous 4-kHz octave band noise exposure. ABRs were obtained immediately after noise exposure and weekly for 3 wk. After euthanization, cochlear hair cell counts were obtained and analyzed. ALCAR administration reduced noise-induced threshold shifts. Three weeks after noise exposure, no threshold shift at 2 to 4 kHz and <10 dB threshold shifts were seen at 6 to 8 kHz in ALCAR-treated animals compared with 30 to 35 dB in control animals. ALCAR treatment reduced both inner and outer hair cell loss. OHC loss averaged <10% for the 4- to 10-kHz region in ALCAR-treated animals and 60% in saline-injected-noise-exposed control animals. Noise-induced threshold shifts were also reduced in carbamathione-treated animals. At 3 wk, threshold shifts averaged 15 dB or less at all frequencies in treated animals and 30 to 35 dB in control animals. Averaged OHC losses were 30% to 40% in carbamathione-treated animals and 60% in control animals. IHC losses were 5% in the 4- to 10-kHz region in treated animals and 10% to 20% in control animals. MET administration reduced noise-induced threshold shifts. ANOVA revealed a significant difference (<.001). Mean OHC and IHC losses were also significantly reduced (<.001). These data lend further support to the growing body of evidence that oxidative stress, generated in part by glutamate excitotoxicity, impaired mitochondrial function and GSH depletion causes cochlear injury induced by noise. Enhancing the cellular

oxidative stress defense pathways in the cochlea eliminates noise-induced cochlear injury. The data also suggest strategies for therapeutic intervention to reduce NIHL clin.

IT **348-67-4**, D-Methionine
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enhancing intrinsic cochlear stress defenses to reduce **noise** -induced hearing loss)

RN 348-67-4 CAPLUS
CN D-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 144 THERE ARE 144 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L77 ANSWER 4 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 2001:537491 CAPLUS
DOCUMENT NUMBER: 135:117260
TITLE: Therapeutic use of D-methionine to reduce the toxicity of **ototoxic** drugs, **noise**, and radiation
INVENTOR(S): Campbell, Kathleen C. M.
PATENT ASSIGNEE(S): Southern Illinois University School of Medicine, USA
SOURCE: U.S., 23 pp., Cont.-in-part of U.S. 6,187,817.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6265386	B1	20010724	US 1998-57065	19980408
US 6187817	B1	20010213	US 1997-942845	19971002
PT 1019036	T	20031128	PT 1998-915362	19980408
ES 2202834	T3	20040401	ES 1998-915362	19980408
US 2002019443	A1	20020214	US 2001-911195	20010723
US 2004110719	A1	20040610	US 2003-694448	20031027
US 2004127568	A1	20040701	US 2003-694432	20031027

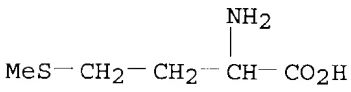
PRIORITY APPLN. INFO.:
US 1997-942845 A2 19971002
US 1996-27750P P 19961003
US 1998-57065 A2 19980408
US 2001-911195 A1 20010723

ED Entered STN: 25 Jul 2001
AB Methods of preventing or reducing hearing or balance loss, damage to ear cells, wt. loss, gastrointestinal toxicity, neurotoxicity, alopecia, and prolonging survival in patients undergoing treatment with therapeutically effective amts. of platinum-contg. chemotherapeutic agents such as cisplatin are provided. Methods are also provided for preventing or reducing such symptoms in patients undergoing treatment with loop diuretics, aminoglycoside antibiotics, iron chelating agents, quinine, and quinidine, or those who have been exposed to toxic levels of noise or radiation. These methods comprise administering an effective amt. of a methionine protective agent, such as D-methionine, prior to,

simultaneously with, or subsequently to administration of the platinum-contg. chemotherapeutic agent, loop diuretic agent, etc., or exposure to noise or radiation. Combinations of these time periods can also be employed.

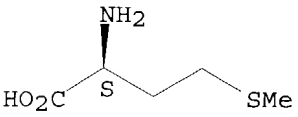
IT **59-51-8**, Methionine **63-68-3**, L-Methionine, biological studies **348-67-4**, D-Methionine **1319-79-5** **6094-76-4**, Homomethionine **13073-35-3**, Ethionine **29908-03-0**, S-Adenosyl-L-methionine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic use of D-methionine and related compds. to reduce toxicity of **ototoxic** drugs, **noise**, platinum-contg. antitumor drugs, and radiation)

RN 59-51-8 CAPLUS
CN Methionine (9CI) (CA INDEX NAME)



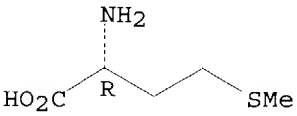
RN 63-68-3 CAPLUS
CN L-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry.

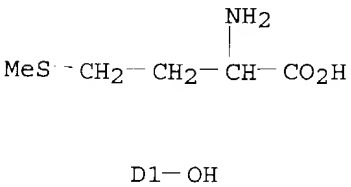


RN 348-67-4 CAPLUS
CN D-Methionine (9CI) (CA INDEX NAME)

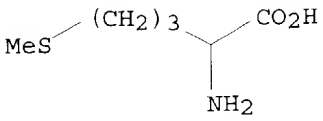
Absolute stereochemistry. Rotation (+).



RN 1319-79-5 CAPLUS
CN L-Methionine, hydroxy- (9CI) (CA INDEX NAME)

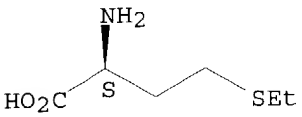


RN 6094-76-4 CAPLUS
CN Norvaline, 5-(methylthio)- (9CI) (CA INDEX NAME)



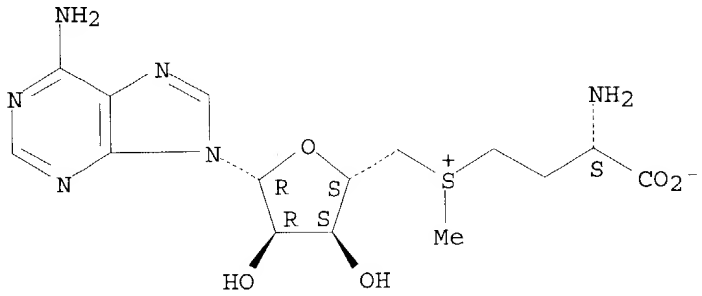
RN 13073-35-3 CAPLUS
CN L-Homocysteine, S-ethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 29908-03-0 CAPLUS
CN Adenosine, 5'-[[(3S)-3-amino-3-carboxypropyl]methylsulfonio]-5'-deoxy-, inner salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L77 ANSWER 5 OF 18 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 1999:249071 CAPLUS
DOCUMENT NUMBER: 130:262147
TITLE: Use of D-methionine or other methionine compound to reduce the toxicity of **ototoxic** drugs, **noise**, and radiation
INVENTOR(S): Campbell, Kathleen C. M.
PATENT ASSIGNEE(S): Southern Illinois University, USA
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9917765	A1	19990415	WO 1998-US6960	19980408

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

US 6187817	B1	20010213	US 1997-942845	19971002
CA 2303901	AA	19990415	CA 1998-2303901	19980408
AU 9869568	A1	19990427	AU 1998-69568	19980408
AU 753039	B2	20021003		
EP 1019036	A1	20000719	EP 1998-915362	19980408
EP 1019036	B1	20030625		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

JP 2001518499	T2	20011016	JP 2000-514636	19980408
AT 243511	E	20030715	AT 1998-915362	19980408
PT 1019036	T	20031128	PT 1998-915362	19980408
ES 2202834	T3	20040401	ES 1998-915362	19980408

PRIORITY APPLN. INFO.:	US 1997-942845	A	19971002
	US 1996-27750P	P	19961003
	WO 1998-US6960	W	19980408

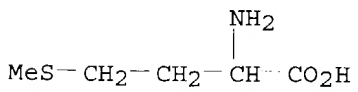
OTHER SOURCE(S): MARPAT 130:262147

ED Entered STN: 23 Apr 1999

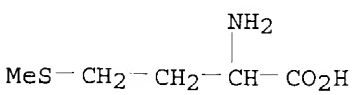
AB Methods of preventing or reducing hearing or balance loss, damage to ear cells, wt. loss, gastrointestinal toxicity, neurotoxicity, alopecia, and prolonging survival in patients undergoing treatment with therapeutically effective amts. of platinum-contg. chemotherapeutic agents, e.g. cisplatin, are provided. Methods are also provided for preventing or reducing such symptoms in patients undergoing treatment with loop diuretics, aminoglycoside antibiotics, iron chelating agents, quinine, and quinidine, or those who have been exposed to toxic levels of noise or radiation. These methods comprise administering an effective amt. of a methionine protective agent, e.g. D-methionine, prior to, simultaneously with, or subsequently to administration of the platinum-contg. chemotherapeutic agent, loop diuretic agent, etc., or exposure to noise or radiation. Combinations of these time periods can also be employed.

IT **59-51-8**, Methionine **59-51-8D**, Methionine, compds.
63-68-3, L-Methionine, biological studies **63-68-3D**, L-Methionine, derivs., biological studies **348-67-4**, D-Methionine **348-67-4D**, D-Methionine, derivs. **1319-79-5** **13073-35-3**, Ethionine **29908-03-0**, S-Adenosyl-L-methionine
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methionine compds. to reduce toxicity of **ototoxic** drugs, **noise**, and radiation)

RN 59-51-8 CAPLUS
CN Methionine (9CI) (CA INDEX NAME)

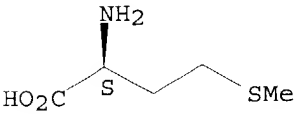


RN 59-51-8 CAPLUS
CN Methionine (9CI) (CA INDEX NAME)



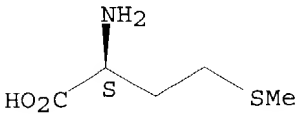
RN 63-68-3 CAPLUS
CN L-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



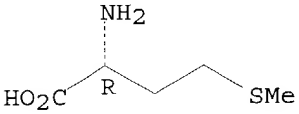
RN 63-68-3 CAPLUS
CN L-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry.



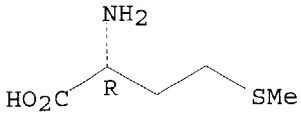
RN 348-67-4 CAPLUS
CN D-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

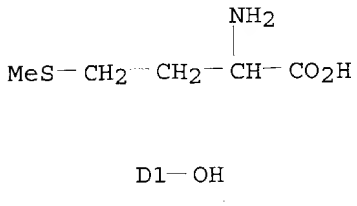


RN 348-67-4 CAPLUS
CN D-Methionine (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

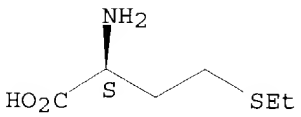


RN 1319-79-5 CAPLUS
CN L-Methionine, hydroxy- (9CI) (CA INDEX NAME)



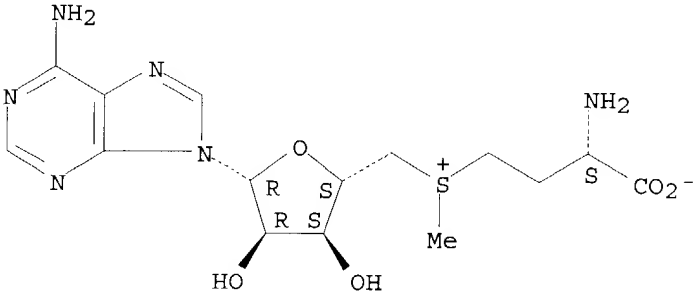
RN 13073-35-3 CAPLUS
CN L-Homocysteine, S-ethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 29908-03-0 CAPLUS
CN Adenosine, 5'-[[(3S)-3-amino-3-carboxypropyl]methylsulfonio]-5'-deoxy-, inner salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L77 ANSWER 6 OF 18 MEDLINE on STN
ACCESSION NUMBER: 1998186668 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9518561
TITLE: Role of glutathione in protection against noise-induced hearing loss.
AUTHOR: Yamasoba T; Nuttall A L; Harris C; Raphael Y; Miller J M
CORPORATE SOURCE: Kresge Hearing Research Institute, The University of Michigan, 1301 East Ann Street, Ann Arbor, MI 48109-0506, USA.
CONTRACT NUMBER: DC00105 (NIDCD)
SOURCE: Brain research, (1998 Feb 16) 784 (1-2) 82-90. Journal code: 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980507
Last Updated on STN: 20000303
Entered Medline: 19980430

ABSTRACT:
A potential mechanism of hearing loss due to acoustic overstimulation is the generation of reactive oxygen species (ROS). ROS not removed by antioxidant defenses could be expected to cause significant damage to the sensory cells of the cochlea. We studied the influence of the antioxidant glutathione (GSH) on noise-induced hearing loss by using l-buthionine-[S,R]-sulfoximine (BSO), an inhibitor of GSH synthesis, and 2-oxothiazolidine-4-carboxylate (OTC), a cysteine prodrug, which promotes rapid restoration of GSH when GSH is acutely depleted. Pigmented female guinea pigs were exposed to broadband noise (102 dB SPL, 3 h/day, 5 days) while receiving daily injections of BSO, OTC, or saline. By weeks 2 and 3 after noise exposure, BSO-treated animals showed significantly

greater threshold shifts above 12 kHz than saline-treated subjects, whereas OTC-treated animals showed significantly smaller threshold shifts at 12 kHz than controls. Histologically assessed noise-induced damage to the organ of Corti, predominantly basal turn row 1 outer hair cells, was most pronounced in BSO-treated animals. High performance liquid chromatographic analysis showed that OTC significantly increased cysteine levels, but not GSH levels, in the cochlea. These findings show that GSH inhibition increases the susceptibility of the cochlea to noise-induced damage and that replenishing GSH, presumably by enhancing availability of cysteine, attenuates noise-induced cochlear damage.

CONTROLLED TERM: Check Tags: Female; Support, U.S. Gov't, P.H.S.
Animals
*Antioxidants: TU, therapeutic use
Auditory Threshold
Buthionine Sulfoximine: TU, therapeutic use
Chromatography, High Pressure Liquid
Cochlea: DE, drug effects
Cochlea: ME, metabolism
Cochlea: PA, pathology
Cysteine: ME, metabolism
Evoked Potentials, Auditory, Brain Stem: DE, drug effects
Evoked Potentials, Auditory, Brain Stem: PH, physiology
Glutathione: ME, metabolism
*Glutathione: PH, physiology
Guinea Pigs
Hearing Loss, Noise-Induced: PA, pathology
***Hearing Loss, Noise-Induced: PC, prevention & control**
*Prodrugs: TU, therapeutic use
*Thiazoles: TU, therapeutic use
CAS REGISTRY NO.: 19750-45-9 (2-oxothiazolidine-4-carboxylic acid); **5072-26-4 (Buthionine Sulfoximine)**; 52-90-4 (Cysteine); 70-18-8 (Glutathione)
CHEMICAL NAME: 0 (Antioxidants); 0 (Prodrugs); 0 (Thiazoles)

L77 ANSWER 7 OF 18 MEDLINE on STN
ACCESSION NUMBER: 91291461 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2064810
TITLE: Effects of blast wave on methionine-enkephalin-like substance (MES) in guinea pig cochleas.
AUTHOR: Liu W
CORPORATE SOURCE: Xijing Hospital, Fourth Military Medical University, Xian.
SOURCE: Zhonghua er bi yan hou ke za zhi, (1991) 26 (2) 67-9, 124.
Journal code: 16210350R. ISSN: 0412-3948.
PUB. COUNTRY: China
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Chinese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199108
ENTRY DATE: Entered STN: 19910901
Last Updated on STN: 19910901
Entered Medline: 19910812

ABSTRACT:
Methionine-enkephalin-like substance in the Corti's organs of guinea pigs with blast trauma-induced deafness was found to be lowered. The most serious changes occurred in the second turn 7 days after the exposure, MEE was then obviously elevated and almost totally recovered at the 23rd day. The transient changes of MEE suggest a reversible decrease of methionine-enkephalin (ME) which might be a neural transmitter within the olivocochlear bundle. The decrease of ME would possibly injure the resistance of hearing organ to further acoustic stimulation.
CONTROLLED TERM: Check Tags: Female; Male; Support, Non-U.S. Gov't

Animals
*Blast Injuries: ME, metabolism
English Abstract
*Enkephalin, Methionine: AA, analogs & derivatives
Enkephalin, Methionine: ME, metabolism
Explosions
Guinea Pigs
***Hearing Loss, Noise-Induced: ME, metabolism**
Organ of Corti: IN, injuries
*Organ of Corti: ME, metabolism
CAS REGISTRY NO.: **58569-55-4 (Enkephalin, Methionine)**
CHEMICAL NAME: 0 (enkephalin-Met, like substances)

L77 ANSWER 8 OF 18 MEDLINE on STN
ACCESSION NUMBER: 88026318 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3664268
TITLE: Effect of noise level on the Met-enkephalin content of the guinea pig cochlea.
AUTHOR: Eybalin M; Rebillard G; Jarry T; Cupo A
CORPORATE SOURCE: I.N.S.E.R.M.-U.254, Universite de Montpellier II, CHR Hopital St. Charles, France.
SOURCE: Brain research, (1987 Aug 18) 418 (1) 189-92.
Journal code: 0045503. ISSN: 0006-8993.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198712
ENTRY DATE: Entered STN: 19900305
Last Updated on STN: 19900305
Entered Medline: 19871209

ABSTRACT:
Using a highly sensitive and specific radioimmunoassay for Met-enkephalin, we have monitored in two series of experiments the changes of the Met-enkephalin content of guinea pig cochleas following a 60 min exposure to different intensities of white noise (70 dB SPL, 90 dB SPL, 110 dB SPL). Our results indicate that the Met-enkephalin content was significantly lower after noise exposures than after exposure to the silence of a sound attenuated chamber. After a stimulation at 70 dB SPL, the levels of Met-enkephalin were 70% (series I) and 61% (series II) of those obtained after a period of silence. After a 110 dB SPL stimulation, these values fell to 41% (series I) and 55% (series II) of those in silence. These results strengthen the hypothesis that enkephalins are olivocochlear neuroactive substances. They suggest that the enkephalin-containing lateral olivocochlear system discharges with noise stimuli of moderate intensity.

CONTROLLED TERM: Acoustic Stimulation
Animals
Auditory Pathways: ME, metabolism
Auditory Pathways: PH, physiology
*Cochlea: ME, metabolism
Cochlea: PH, physiology
*Enkephalin, Methionine: ME, metabolism
Enkephalin, Methionine: PH, physiology
Guinea Pigs
***Noise**
Radioimmunoassay
CAS REGISTRY NO.: **58569-55-4 (Enkephalin, Methionine)**

L77 ANSWER 9 OF 18 MEDLINE on STN
ACCESSION NUMBER: 70290611 MEDLINE
DOCUMENT NUMBER: PubMed ID: 5458726
TITLE: Inferior colliculus lesion and audiogenic seizure

susceptibility.
AUTHOR: Wada J A; Terao A; White B; Jung E
SOURCE: Experimental neurology, (1970 Aug) 28 (2) 326-32.
Journal code: 0370712. ISSN: 0014-4886.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197011
ENTRY DATE: Entered STN: 19900101
Last Updated on STN: 19900101
Entered Medline: 19701105
CONTROLLED TERM: Check Tags: Female; Male
Animals
*Behavior, Animal
Cats
*Convulsions: GE, genetics
*Corpora Quadrigemina: PH, physiology
Laterality
Methionine Sulfoximine: PD, pharmacology
Noise
Pentylenetetrazole: PD, pharmacology
Rats
Thiosemicarbazones: PD, pharmacology
CAS REGISTRY NO.: **1982-67-8 (Methionine Sulfoximine)**; 54-95-5 (Pentylenetetrazole)
CHEMICAL NAME: 0 (Thiosemicarbazones)

L77 ANSWER 10 OF 18 MEDLINE on STN
ACCESSION NUMBER: 68012724 MEDLINE
DOCUMENT NUMBER: PubMed ID: 6053658
TITLE: Transient reduction of audiogenic susceptibility by methionine sulfoximine in genetically sensitive rats.
AUTHOR: Wada J A; Asakura T; Ikeda H
SOURCE: Experimental neurology, (1967 Nov) 19 (3) 346-9.
Journal code: 0370712. ISSN: 0014-4886.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 196712
ENTRY DATE: Entered STN: 19900101
Last Updated on STN: 19900101
Entered Medline: 19671219
CONTROLLED TERM: Check Tags: Female; Male
Animals
*Auditory Perception: DE, drug effects
Hypothermia, Induced
*Methionine: PD, pharmacology
Methionine Sulfoximine: PD, pharmacology
Noise
Rats
CAS REGISTRY NO.: **1982-67-8 (Methionine Sulfoximine); 63-68-3 (Methionine)**

L77 ANSWER 11 OF 18 EMBASE
on STN
ACCESSION NUMBER: 2004245253 EMBASE
TITLE: Oxidants vs. antioxidants: The war within - And our cells are at stake.
AUTHOR: Campbell K.C.M.
CORPORATE SOURCE: Dr. K.C.M. Campbell, Audiology Research, Southern Illinois

University, School of Medicine in Springfield, Springfield, IL, United States
SOURCE: Hearing Journal, (2004) 57/5 (10-17).
ISSN: 0745-7472 CODEN: HJEOAY
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 011 Otorhinolaryngology
029 Clinical Biochemistry
LANGUAGE: English

CONTROLLED TERM: Medical Descriptors:
*hearing
*hearing loss: ET, etiology
*hearing loss: PC, prevention
drug safety
drug efficacy
food and drug administration
drug approval
noise injury
diet
inner ear
presbyacusis
patient care
electron transport
lipid peroxidation
cochlea
auditory threshold
diet supplementation
oxidative stress
nutritional value
nutrient content
human
article
Drug Descriptors:
*oxidizing agent
*antioxidant
non prescription drug
magnesium
methionine
acetylcysteine
resveratrol
free radical: EC, endogenous compound
reactive oxygen metabolite: EC, endogenous compound
lipid peroxide: EC, endogenous compound
glutathione: EC, endogenous compound
superoxide dismutase: EC, endogenous compound
catalase: EC, endogenous compound
glutathione peroxidase: EC, endogenous compound
CAS REGISTRY NO.: (magnesium) 7439-95-4; (methionine) **59-51-8**, **63-68-3**, **7005-18-7**; (acetylcysteine) 616-91-1; (resveratrol) 501-36-0; (glutathione) 70-18-8; (superoxide dismutase) 37294-21-6, 9016-01-7, 9054-89-1; (catalase) 9001-05-2; (glutathione peroxidase) 9013-66-5

L77 ANSWER 12 OF 18 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003170405 EMBASE
TITLE: Pharmacologic manipulation of the labyrinth with novel and traditional agents delivered to the inner ear.
AUTHOR: Seidman M.D.; Van De Water T.R.
CORPORATE SOURCE: Dr. M.D. Seidman, Department of Otologic Surgery, Henry Ford Medical Center, 6777 W. Maple Rd., West Bloomfield, MI

48322, United States. mseidma1@hfhs.org
SOURCE: Ear, Nose and Throat Journal, (1 Apr 2003) 82/4 (276-300).
Refs: 207
ISSN: 0145-5613 CODEN: ENTJDO
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 011 Otorhinolaryngology
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
We describe the methodology and rationale behind the delivery of therapeutic medicines to the inner ear. The inner ear has long been impervious to pharmacologic manipulation. This is most likely the result of a protective mechanism called the blood-labyrinth barrier, whose function closely resembles that of the blood-brain barrier. This protective barrier impedes the clinician's ability to treat inner ear diseases with systemically administered medications. Since 1935, otolaryngologists have attempted to manipulate the inner ear with transtympanically injected medicines. Success has varied widely, but medicinal ablation of vestibular function can be achieved in this manner. Unfortunately, the auditory system is also at great risk from any medicine that is delivered to the inner ear via the middle ear. Over the past 10 years, significant improvements in drug delivery have allowed for more "titratable" treatment, which has reduced (but not eliminated) the risk of permanent hearing loss. In this article, we discuss both novel and time-tested methods of delivering medicines to the inner ear. We also review the classes of medications that alter inner ear function and the attendant risks of such treatments.

CONTROLLED TERM: Medical Descriptors:
*inner ear disease: DT, drug therapy
*inner ear disease: ET, etiology
*inner ear disease: TH, therapy
*drug delivery system
*Meniere disease: DT, drug therapy
*tinnitus: DT, drug therapy
*tinnitus: ET, etiology
*tinnitus: TH, therapy
inner ear
technique
systemic therapy
vestibular function
auditory system
risk factor
middle ear
titrimetry
hearing loss: SI, side effect
ototoxicity: SI, side effect
cochlea fenestra
perception deafness: DT, drug therapy
perception deafness: ET, etiology
cochlea blood flow
drug effect
drug efficacy
auditory threshold shift
drug tissue level
treatment outcome
permeability barrier
blood labyrinth barrier
neuroprotection

noise injury: ET, etiology
Parkinson disease: DT, drug therapy
Alzheimer disease: DT, drug therapy
drug safety
drug tolerability
taste disorder: SI, side effect
vertigo: SI, side effect
headache: SI, side effect
hot flush: SI, side effect
protein restriction
disease association
breast cancer: DT, drug therapy
human
nonhuman
rat
major clinical study
clinical trial
double blind procedure
single blind procedure
animal experiment
controlled study
animal tissue
newborn
article
Drug Descriptors:
aminoglycoside antibiotic agent: AE, adverse drug reaction
aminoglycoside antibiotic agent: DT, drug therapy
aminoglycoside antibiotic agent: PR, pharmaceutics
aminoglycoside antibiotic agent: PD, pharmacology
aminoglycoside antibiotic agent: TY, intratympanic drug administration
streptomycin: AE, adverse drug reaction
streptomycin: DT, drug therapy
streptomycin: PD, pharmacology
gentamicin: AE, adverse drug reaction
gentamicin: DT, drug therapy
gentamicin: PR, pharmaceutics
gentamicin: PD, pharmacology
gentamicin: TY, intratympanic drug administration
corticosteroid: CB, drug combination
corticosteroid: CR, drug concentration
corticosteroid: DT, drug therapy
corticosteroid: PD, pharmacology
corticosteroid: TY, intratympanic drug administration
corticosteroid: PO, oral drug administration
dexamethasone: CB, drug combination
dexamethasone: DT, drug therapy
dexamethasone: PD, pharmacology
dexamethasone: TY, intratympanic drug administration
methylprednisolone: CB, drug combination
methylprednisolone: DT, drug therapy
methylprednisolone: PD, pharmacology
methylprednisolone: TY, intratympanic drug administration
lidocaine: CB, drug combination
lidocaine: DT, drug therapy
lidocaine: PD, pharmacology
lidocaine: TY, intratympanic drug administration
lidocaine: IV, intravenous drug administration
hyaluronidase: CB, drug combination
hyaluronidase: DT, drug therapy
hyaluronidase: PD, pharmacology
hyaluronidase: TY, intratympanic drug administration

antidepressant agent: DT, drug therapy
antidepressant agent: PD, pharmacology
antidepressant agent: PO, oral drug administration
AMPA receptor: EC, endogenous compound
n methyl dextro aspartic acid receptor: EC, endogenous compound
kainic acid receptor: EC, endogenous compound
kynurenic acid: PD, pharmacology
glutamate receptor antagonist: AE, adverse drug reaction
glutamate receptor antagonist: CT, clinical trial
glutamate receptor antagonist: CR, drug concentration
glutamate receptor antagonist: DV, drug development
glutamate receptor antagonist: DT, drug therapy
glutamate receptor antagonist: PD, pharmacology
glutamate receptor antagonist: IV, intravenous drug administration
glutamate receptor antagonist: PO, oral drug administration
memantine: AE, adverse drug reaction
memantine: CT, clinical trial
memantine: DV, drug development
memantine: DT, drug therapy
memantine: PD, pharmacology
caroverine: AE, adverse drug reaction
caroverine: CT, clinical trial
caroverine: CR, drug concentration
caroverine: DV, drug development
caroverine: DT, drug therapy
caroverine: PD, pharmacology
caroverine: IV, intravenous drug administration
AMPA receptor antagonist: AE, adverse drug reaction
AMPA receptor antagonist: CT, clinical trial
AMPA receptor antagonist: CR, drug concentration
AMPA receptor antagonist: DV, drug development
AMPA receptor antagonist: DT, drug therapy
AMPA receptor antagonist: PD, pharmacology
AMPA receptor antagonist: IV, intravenous drug administration
magnesium: CT, clinical trial
magnesium: CR, drug concentration
magnesium: DV, drug development
magnesium: DT, drug therapy
magnesium: PR, pharmaceutics
magnesium: PD, pharmacology
magnesium: PO, oral drug administration
anxiolytic agent: DT, drug therapy
calpain: EC, endogenous compound
leupeptin: DV, drug development
leupeptin: DO, drug dose
leupeptin: PD, pharmacology
leupeptin: IM, intramuscular drug administration
leupeptin: TY, intratympanic drug administration
leupeptin: PO, oral drug administration
allopurinol: PD, pharmacology
superoxide dismutase macrogol: PD, pharmacology
glutathione: EC, endogenous compound
cisplatin: AE, adverse drug reaction
cisplatin: DT, drug therapy
etacrynic acid: AE, adverse drug reaction
etacrynic acid: CB, drug combination
kanamycin: AE, adverse drug reaction
kanamycin: CB, drug combination
methionine: PD, pharmacology

intercellular adhesion molecule 1: EC, endogenous compound
neurotrophic factor: PD, pharmacology

CAS REGISTRY NO.: (streptomycin) 57-92-1; (gentamicin) 1392-48-9, 1403-66-3, 1405-41-0; (dexamethasone) 50-02-2; (methylprednisolone) 6923-42-8, 83-43-2; (lidocaine) 137-58-6, 24847-67-4, 56934-02-2, 73-78-9; (hyaluronidase) 9001-54-1, 9055-18-9; (kynurenic acid) 492-27-3; (memantine) 19982-08-2, 41100-52-1; (caroverine) 23465-76-1, 55750-05-5; (magnesium) 7439-95-4; (calpain) 78990-62-2; (leupeptin) 54577-99-0; (allopurinol) 315-30-0; (glutathione) 70-18-8; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (etacrynic acid) 58-54-8; (kanamycin) 11025-66-4, 61230-38-4, 8063-07-8; (methionine) **59-51-8**, **63-68-3**, **7005-18-7**; (intercellular adhesion molecule 1) 126547-89-5

L77 ANSWER 13 OF 18 EMBASE
on STN

ACCESSION NUMBER: 2001194322 EMBASE
TITLE: Patent issued for hearing loss prevention treatment.
SOURCE: Hearing Journal, (2001) 54/4 (7-8).
ISSN: 0745-7472 CODEN: HJEOAY
COUNTRY: United States
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 004 Microbiology
008 Neurology and Neurosurgery
011 Otorhinolaryngology
027 Biophysics, Bioengineering and Medical Instrumentation
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English

CONTROLLED TERM: Medical Descriptors:
***hearing loss: DI, diagnosis**
***hearing loss: DT, drug therapy**
***hearing loss: PC, prevention**
***hearing loss: TH, therapy**
*otitis media: DT, drug therapy
*otitis media: PC, prevention
noise
United States
clinical research
hair cell
exposure
drug mixture
drug efficacy
patent
cancer: DT, drug therapy
acquired immune deficiency syndrome: DT, drug therapy
neurologic disease: DT, drug therapy
screening
medical instrumentation
hearing aid
drug formulation
alpha hemolytic Streptococcus
nuclear magnetic resonance imaging
sex difference
human
nonhuman
male
female

animal experiment
animal model
controlled study
newborn
child
note
Drug Descriptors:
antioxidant: DV, drug development
antioxidant: DT, drug therapy
methionine
acetylcysteine: DT, drug therapy
antibiotic agent: DT, drug therapy
placebo
probiotic agent: DV, drug development
probiotic agent: PR, pharmaceutics
CAS REGISTRY NO.: (methionine) **59-51-8, 63-68-3, 7005-18-7**; (acetylcysteine) 616-91-1

L77 ANSWER 14 OF 18 EMBASE
on STN
ACCESSION NUMBER: 1998012701 EMBASE
TITLE: Drug-induced hearing loss: A worldwide problem.
AUTHOR: Arkaravichien W.; Schacht J.
CORPORATE SOURCE: W. Arkaravichien, Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen, Thailand
SOURCE: International Medical Journal, (1997) 4/4 (243-251).
Refs: 96
ISSN: 1341-2051 CODEN: IMJOFS
COUNTRY: Japan
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
011 Otorhinolaryngology
017 Public Health, Social Medicine and Epidemiology
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
A large number of drugs in common clinical practice may adversely affect hearing and balance in patients. These 'ototoxic' drugs belong to such diverse therapeutic classes as antimicrobial agents (aminoglycoside antibiotics, macrolides), loop diuretics, antimalarials, non-steroidal anti-inflammatory and antineoplastic agents. Their toxic effects result from pathological changes in inner ear tissues, producing tinnitus, hearing loss, or vestibular dysfunction including vertigo and ataxia. The disturbances may be transient, as in the case of diuretics and saiicylates. Several therapeutics, however, will cause irreversible damage, most notably, aminoglycoside antibiotics and cisplatin. This review describes the pathological changes, cellular mechanism(s), clinical manifestation and risk factors associated with the most prominent ototoxic agents. Such knowledge will enable the physician to seek methods to prevent or minimize the hazards associated with these drugs. Furthermore, recent advances in pharmacological prevention of hearing loss by cisplatin and aminoglycoside antibiotics are discussed.

CONTROLLED TERM: Medical Descriptors:
***ototoxicity: DT, drug therapy**
***ototoxicity: EP, epidemiology**
***ototoxicity: PC, prevention**
***ototoxicity: SI, side effect**
***ototoxicity: DM, disease management**

***hearing loss: DI, diagnosis**
***hearing loss: DT, drug therapy**
***hearing loss: EP, epidemiology**
***hearing loss: PC, prevention**
***hearing loss: SI, side effect**
***hearing loss: DM, disease management**
drug toxicity: SI, side effect
pathology
inner ear
toxicity: SI, side effect
vestibular disorder: SI, side effect
vertigo: SI, side effect
ataxia: SI, side effect
risk factor
ear protection
kidney disease: ET, etiology
drug contraindication
drug potentiation
cochlea
hair cell
noise
genetic susceptibility
tinnitus: SI, side effect
iron chelation
neuropathy: SI, side effect
nephrotoxicity: SI, side effect
perception deafness: SI, side effect
drug choice
drug infusion
disease predisposition
high risk patient
patient monitoring
pregnancy
human
nonhuman
oral drug administration
topical drug administration
review
Drug Descriptors:
*antiinfective agent: AE, adverse drug reaction
*loop diuretic agent: AE, adverse drug reaction
*loop diuretic agent: CB, drug combination
*loop diuretic agent: DO, drug dose
*loop diuretic agent: IT, drug interaction
*loop diuretic agent: PD, pharmacology
*antimalarial agent: AE, adverse drug reaction
*antimalarial agent: DO, drug dose
*antimalarial agent: PD, pharmacology
*nonsteroid antiinflammatory agent: AE, adverse drug reaction
*antineoplastic agent: AE, adverse drug reaction
aminoglycoside: AE, adverse drug reaction
aminoglycoside: CB, drug combination
aminoglycoside: DO, drug dose
aminoglycoside: IT, drug interaction
aminoglycoside: PD, pharmacology
aminoglycoside: PE, pharmacoeconomics
macrolide: AE, adverse drug reaction
salicylic acid: AE, adverse drug reaction
salicylic acid: DO, drug dose
salicylic acid: PD, pharmacology
cisplatin: AE, adverse drug reaction

cisplatin: DO, drug dose
cisplatin: IT, drug interaction
cisplatin: PD, pharmacology
gentamicin: AE, adverse drug reaction
gentamicin: CB, drug combination
gentamicin: CR, drug concentration
gentamicin: DO, drug dose
gentamicin: IT, drug interaction
gentamicin: PD, pharmacology
vancomycin: AE, adverse drug reaction
vancomycin: CB, drug combination
vancomycin: DO, drug dose
vancomycin: IT, drug interaction
etacrynic acid: AE, adverse drug reaction
etacrynic acid: IT, drug interaction
antibiotic agent: AE, adverse drug reaction
antibiotic agent: AD, drug administration
antibiotic agent: CB, drug combination
antibiotic agent: IT, drug interaction
unindexed drug: AE, adverse drug reaction
unindexed drug: CB, drug combination
unindexed drug: DO, drug dose
unindexed drug: IT, drug interaction
unindexed drug: PD, pharmacology
chelating agent: AE, adverse drug reaction
chelating agent: DO, drug dose
chelating agent: DT, drug therapy
chelating agent: PD, pharmacology
chloramphenicol: AE, adverse drug reaction
methionine: AD, drug administration
methionine: DT, drug therapy
diethyldithiocarbamic acid: DT, drug therapy
deferoxamine: DT, drug therapy
deferoxamine: PD, pharmacology

CAS REGISTRY NO.: (salicylic acid) 63-36-5, 69-72-7; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (gentamicin) 1392-48-9, 1403-66-3, 1405-41-0; (vancomycin) 1404-90-6, 1404-93-9; (etacrynic acid) 58-54-8; (chloramphenicol) 134-90-7, 2787-09-9, 56-75-7; (methionine) **59-51-8**, **63-68-3**, **7005-18-7**; (diethyldithiocarbamic acid) 147-84-2, 148-18-5, 3699-30-7, 392-74-5; (deferoxamine) 70-51-9

L77 ANSWER 15 OF 18 CONFSCI COPYRIGHT 2004 CSA on STN
ACCESSION NUMBER: 2003:60579 CONFSCI
DOCUMENT NUMBER: 03-060579
TITLE: D-**methionine otoprotection** from cisplatin-induced, aminoglycoside-induced, and **noise**-induced **hearing** loss: Correlation of cochlear oxidative state to ABR findings
AUTHOR: Campbell, K.C.M.; Meech, R.P.; Rybak, L.P.; Hughes, L.F.
SOURCE: Int'l Evoked Response Audiometry Study Group, Perez de Rozas 8ES-38004 Santa Cruz, Tenerife, Spain; phone: 34 (922) 27 54 88; fax: 34 (922) 27 03 64; email: info@ierasg-2003.org; URL: www.ierasg-2003.org. Paper No. 1.c.4.
Meeting Info.: 000 7012: International Evoked Response Audiometry Study Group 18th Biennial Symposium (0007012). Puerto de la Cruz (Spain). 8-13 Jun 2003. Universidad de La Laguna, Consejeria de Sanidad y Consumo del Gobierno de Canarias, Cabildo de Santa Cruz de Tenerife, Ayuntamiento del Puerto de la Cruz, Ayuntamiento de La Laguna, Ayuntamiento de La Orotava.

DOCUMENT TYPE: Conference
FILE SEGMENT: DCCP
LANGUAGE: English
CLASSIFICATION: 2000 BIOLOGY GENERAL

L77 ANSWER 16 OF 18 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2003-645977 [61] WPIDS
DOC. NO. CPI: C2003-176693
TITLE: Composition useful in the amelioration of **hearing** loss induced by exposure to an **ototoxic** agent comprises at least one **otoprotectant**.
DERWENT CLASS: B05
INVENTOR(S): KIL, J; LYNCH, E D
PATENT ASSIGNEE(S): (SOUN-N) SOUND PHARM INC
COUNTRY COUNT: 102
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2003057207	A1	20030717	(200361)*	EN	16	A61K031-195
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW						
US 2003162747	A1	20030828	(200363)			A61K031-724
AU 2003202219	A1	20030724	(200421)			A61K031-195

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003057207	A1	WO 2003-US308	20030103
US 2003162747	A1 Provisional	US 2002-345813P	20020104
		US 2003-337251	20030103
AU 2003202219	A1	AU 2003-202219	20030103

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003202219	A1 Based on	WO 2003057207

PRIORITY APPLN. INFO: US 2002-345813P 20020104; US 2003-337251 20030103
INT. PATENT CLASSIF.:
MAIN: A61K031-195; A61K031-724
SECONDARY: A61K031-4162; A61K031-41622; A61K031-519; A61K031-5199; A61K031-7244
BASIC ABSTRACT:
WO2003057207 A UPAB: 20030923
NOVELTY - An **otoprotectant** composition (C1) comprises at least one **otoprotectant** selected from Group A, i.e. 2-phenyl-1,2-benzoisoselenazol-3(2H)-one (ebselen), 6A,6B-diseleninic acid-6A',6B'-selenium bridged beta -cyclodextrin (6-diSeCD) or 2,2'-diseleno-bis- beta -cyclodextrin (2-diSeCD).
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for an **otoprotectant** composition comprising **otoprotectants** selected from Group B and Group C, where Group B is allopurinol, 1-methylallopurinol, 2-methylallopurinol, 5-methylallopurinol,

7-methylallopurinol, 1,5-dimethylallopurinol, 2,5-dimethylallopurinol, 1,7-dimethylallopurinol, 2,7-dimethylallopurinol, 5,7-dimethylallopurinol, 2,5,7-trimethylallopurinol, 1-ethoxycarbonylallopurinol or 1-ethoxycarbonyl-5-methylallopurinol and Group C is **methionine**, N-acetyl-DL-**methionine**, S-adenosylmethionine, cysteine, homocysteine, cysteamine, N-acetylcysteine, glutathione, glutathione ethylester, glutathione diethylester, glutathione triethylester, cystathione, N,N'-diacetyl-L-cystine (DiNAC), 2(R,S)-D-ribo-(1',2',3',4'-tetrahydroxybutyl)-thiazolidine-4(R)-carboxylic acid (RibCys), 2-alkylthiazolidine-2(R,S)-D-ribo-(1',2',3',4'-tetrahydroxybutyl)-thiazolidine (RibCyst) or 2-oxo-L-thiazolidine-4-carboxylic acid (OTCA).

ACTIVITY - Auditory.

8-Week old female rats were exposed to 110dB **noise** at 4 - 16 kHz for 4 hours two times three weeks apart. The animals were tested before and 3 weeks following the repeated **noise** exposure to permanent threshold shift (PTS). A test composition was prepared by dissolving ebselen (4 mg/ml) in 10% dimethylsulfoxide (DMSO) and this was administered to rats at a dosage of 16 mg/kg. About 0.5 ml of ebselen solution was injected intraperitoneally, the day prior to, the day of and the day following each exposure to **noise**. Control group animals were treated with vehicle. The dB shift from baseline for the test/control was: 3/7 (at 4 kHz); 13/25 (at 8 kHz); 14/20 (at 12 kHz) and 32/40 (at 16 kHz) respectively. The results showed that administration of ebselen showed significant reduction in temporary threshold shift (TTS) at 1 day after repeated **noise** exposures compared with controls. The PTS at three weeks after repeated **noise** exposure was reduced in the animals as compared to the controls.

MECHANISM OF ACTION - None given.

USE - The composition is used as and **otoprotectant** for ameliorating **hearing** loss in mammalian subject (e.g. human subject) (claimed) induced by exposure to **ototoxic** agent.

ADVANTAGE - The composition effectively prevents **hearing** loss.

Dwg.0/4

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B04-B03A; B04-C02B1; B05-B01D; B06-D09; B07-F01; B10-A04; B10-B02D; B14-N04

L77 ANSWER 17 OF 18 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2003:833809 SCISEARCH
THE GENUINE ARTICLE: 723VU
TITLE: A peptide inhibitor of c-Jun N-terminal kinase protects against both aminoglycoside and **acoustic** **trauma**-induced auditory hair cell death and **hearing** loss
AUTHOR: Wang J; Van de Water T R; Bonny C; de Ribaupierre F; Puel J L; Zine A (Reprint)
CORPORATE SOURCE: Univ Montpellier 1, INSERM, U583, 71 Rue Navacelles, F-34090 Montpellier, France (Reprint); Univ Montpellier 1, INSERM, U583, F-34090 Montpellier, France; Univ Miami, Ear Inst, Cochlear Implant Res Program, Miami, FL 33136 USA; CHU Vaudois, Div Gen Med, CH-1011 Lausanne, Switzerland; Univ Lausanne, Inst Physiol, CH-1005 Lausanne, Switzerland
COUNTRY OF AUTHOR: France; USA; Switzerland
SOURCE: JOURNAL OF NEUROSCIENCE, (17 SEP 2003) Vol. 23, No. 24, pp. 8596-8607.
Publisher: SOC NEUROSCIENCE, 11 DUPONT CIRCLE, NW, STE 500, WASHINGTON, DC 20036 USA.
ISSN: 0270-6474.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English

REFERENCE COUNT: 49
ABSTRACT:

Hearing loss can be caused by a variety of insults, including ***acoustic*** **trauma** and exposure to **ototoxins**, that principally effect the viability of sensory hair cells via the MAP kinase (MAPK) cell death signaling pathway that incorporates c-Jun N-terminal kinase (JNK).

We evaluated the **otoprotective** efficacy of D-JNKI-1, a cell permeable peptide that blocks the MAPK-JNK signal pathway. The experimental studies included organ cultures of neonatal mouse cochlea exposed to an ***ototoxic*** drug and cochleae of adult guinea pigs that were exposed to either an **ototoxic** drug or **acoustic trauma**. Results obtained from the organ of Corti explants demonstrated that the MAPK-JNK signal pathway is associated with injury and that blocking of this signal pathway prevented apoptosis in areas of aminoglycoside damage. Treatment of the neomycin-exposed organ of Corti explants with D-JNKI-1 completely prevented hair cell death initiated by this **ototoxin**. Results from in vivo studies showed that direct application of D-JNKI-1 into the scala tympani of the guinea pig cochlea prevented nearly all hair cell death and permanent ***hearing*** loss induced by neomycin **ototoxicity**. Local delivery of D-JNKI-1 also prevented **acoustic trauma**-induced permanent **hearing** loss in a dose-dependent manner. These results indicate that the MAPK-JNK signal pathway is involved in both ***ototoxicity*** and **acoustic trauma**-induced hair cell loss and permanent **hearing** loss. Blocking this signal pathway with D-JNKI-1 is of potential therapeutic value for long-term protection of both the morphological integrity and physiological function of the organ of Corti during times of oxidative stress.

CATEGORY: NEUROSCIENCES
SUPPLEMENTARY TERM: neomycin; **ototoxicity**; **acoustic trauma**; **noise**-induced **hearing** loss; apoptosis of hair cells; c-Jun N-terminal kinase (JNK); JNK inhibition; organ of Corti
SUPPL. TERM PLUS: SIGNAL-TRANSDUCTION PATHWAY; GUINEA-PIG; IN-VITRO; INDUCED COCHLEAR; CEP-1347 KT7515; INTENSE **NOISE**; L-**METHIONINE**; RAT ORGAN; JNK; ACTIVATION

REFERENCE(S):

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)
BARR R K	2002	277	10987	J BIOL CHEM
BODNER D	2002	172	81	HEARING RES
BODNER D	2002	112	2057	LARYNGOSCOPE
BONNY C	2001	50	77	DIABETES
BREDBERG G	1968	236	1	ACTA OTOLARYNGOL S S
CHOMCZYNSKI P	1987	162	156	ANAL BIOCHEM
CLERICI W J	1996	98	116	HEARING RES
CODY A R	1980	12	121	SCAND AUDIOL S
CONLON B J	1999	128	40	HEARING RES
DAVIS R J	2000	103	239	CELL
DERIJARD B	1994	76	1025	CELL
DICKENS M	1997	277	693	SCIENCE
FINKEL T	1998	10	248	CURR OPIN CELL BIOL
FORGE A	2000	139	97	HEARING RES
FORGE A	1985	19	171	HEARING RES
GARETZ S L	1994	77	75	HEARING RES
GUPTA S	1995	267	389	SCIENCE
HALAZONETIS T D	1988	55	917	CELL
HARRIS C A	2002	22	103	J NEUROSCI
HIROSE K	1997	104	1	HEARING RES
HU B H	2000	120	19	ACTA OTO-LARYNGOL

HU B H	2002	166	62	HEARING RES
IP Y T	1998	10	205	CURR OPIN CELL BIOL
KYRIAKIS J M	1994	369	156	NATURE
LI G M	2001	22	163	NEUROTOXICOLOGY
MARKGRAF C G	1998	29	152	STROKE
MARONEY A C	1998	18	104	J NEUROSCI
MARONEY A C	2001	276	25302	J BIOL CHEM
MARSHALL C J	1995	80	179	CELL
MELOCHE S	1992	6	845	MOL ENDOCRINOL
NAKAGAWA T	1998	118	530	ACTA OTO-LARYNGOL
NAKAGAWA T	1998	255	127	EUR ARCH OTO-RHINO-L
PIRVOLA U	2000	20	43	J NEUROSCI
PRIUSKA E M	1995	50	1749	BIOCHEM PHARMACOL
PUJOL R	1986	429	29	ACTA OTOLARYNGOL S
RESER D	1999	20	731	NEUROTOXICOLOGY
RUBEN R J	1967	220	1	ACTA OTOLARYNGOL S S
SANDMANN S	2002	135	1951	BRIT J PHARMACOL
SAPORITO M S	1999	288	421	J PHARMACOL EXP THER
TOURNIER C	2000	288	870	SCIENCE
TRAVERSE S	1994	4	694	CURR BIOL
VAGO P	1998	9	431	NEUROREPORT
VIVES E	1997	272	16010	J BIOL CHEM
WANG J	2002	111	635	NEUROSCIENCE
WHITMARSH A J	1998	23	481	TRENDS BIOCHEM SCI
XU Z H	2003	22	252	EMBO J
YLIKOSKI J	2002	166	33	HEARING RES
ZINE A	1998	9	263	NEUROREPORT
ZINE A	1999	38	313	J NEUROBIOL

L77 ANSWER 18 OF 18 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2002:888794 SCISEARCH
THE GENUINE ARTICLE: 607HJ
TITLE: Local administration of antioxidants to the inner ear - Kinetics and distribution
AUTHOR: Laurell G (Reprint); Teixeira M; Sterkers O; Bagger-Sjoback D; Eksborg S; Lidman O; Ferrary E
CORPORATE SOURCE: Karolinska Hosp, Dept Otolaryngol, S-17176 Stockholm, Sweden (Reprint); Univ Paris 07, INSERM, U426, F-75018 Paris, France; Univ Paris 07, Fac Xavier Bichat, F-75018 Paris, France; Karolinska Pharm, S-17176 Stockholm, Sweden; Karolinska Hosp, Ctr Mol Med, S-17176 Stockholm, Sweden
COUNTRY OF AUTHOR: Sweden; France
SOURCE: HEARING RESEARCH, (NOV 2002) Vol. 173, No. 1-2, pp. 198-209.
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS.
ISSN: 0378-5955.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 34
ABSTRACT:

Round window (r.w.) administration of drugs involves the delivery of medication directly into the inner ear via the r.w. membrane, avoiding a systemic effect of the therapy. Earlier experimental studies suggest that a number of antioxidants and scavengers hold promise for ameliorating the tissue damaging capacity of reactive oxygen species in some acquired cochlear disorders. D-**Methionine** and thiourea are two small sulfur-containing molecules with an antioxidative and scavenging effect. The passage through the r.w. of radioactive D-**methionine** and thiourea administered by 1 h infusion to the r.w. was studied in a rat model. Levels of the tracers were measured in scala tympani perilymph (PLT) 17-254 min after r.w. administration.

Both tracers pass the r.w. membrane readily. Peak levels were found in the earliest taken samples after the administration. The radioactivity in PLT of the basal turn reached a peak to about 1.5-1.9% of the irrigating medium radioactivity. Following the r.w. administration, the concentration of radioactive D-**methionine** and thiourea declined with a terminal half-life of 0.57 and 0.77 h, respectively. The distribution of the tracers at the cellular level was analyzed by autoradiography. The most intense expression was found in the lateral wall of the cochlea. It can be postulated that local delivery to the cochlea Of D-**methionine** and thiourea via the r.w. gives high local concentrations of the substances in PLT in the basal turn.

CATEGORY: NEUROSCIENCES; OTORHINOLARYNGOLOGY
SUPPLEMENTARY TERM: pharmacokinetics; autoradiography; scavenger; scala tympani perilymph; lateral wall
SUPPL. TERM PLUS: ROUND WINDOW MEMBRANE; OXYGEN SPECIES GENERATION; INDUCED **HEARING**-LOSS; CISPLATIN **OTOTOXICITY**; HAIR-CELLS; IN-VIVO; PROTECTION; **NOISE**; PERMEABILITY; PERILYMPH

REFERENCE(S):

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)
BAGGERSJOBACK D	1992	54	5	ORL J OTO-RHINO-LARY
BANACLOCHA M M	1999	842	249	BRAIN RES
BRIZEL D M	2000	18	3339	J CLIN ONCOL
CAMPBELL K C M	1996	102	90	HEARING RES
CLERICI W J	1996	101	14	HEARING RES
CLERICI W J	1996	98	116	HEARING RES
DUAN M L	2000	97	7597	P NATL ACAD SCI USA
DUNNE A	1985	20	269	COMPUT METH PROG BIO
EKBORN A	2002	165	53	HEARING RES
ENGEL F	1998	66	343	INFECT IMMUN
GABAIZADEH R	1997	117	232	ACTA OTO-LARYNGOL
GOYCOOLEA M V	1997	36	201	MICROSC RES TECHNIQ
HALLIWELL B	1992	59	1609	J NEUROCHEM
HARA A	1989	42	265	HEARING RES
HARNER S G	1998	108	1446	LARYNGOSCOPE
HU B H	1997	113	198	HEARING RES
HUSMANN K R	1998	125	109	HEARING RES
JACONO A A	1998	117	31	HEARING RES
KAWAUCHI H	1988	457	100	ACTA OTOLARYNGOL S S
LI G M	2001	22	163	NEUROTOXICOLOGY
LUNDMAN L	1992	112	524	ACTA OTO-LARYNGOL
MILLER J M	1994	15	299	AM J OTOL
PARNES L S	1999	109	1	LARYNGOSCOPE S91 2
RAVI R	1995	76	386	PHARMACOL TOXICOL
RILEY C M	1982	1	201	POLYHEDRON
SALT A N	2001	154	88	HEARING RES
SHA S H	2000	142	24	HEARING RES
SPRONG R C	1997	129	470	J LAB CLIN MED
STERKERS O	1982	243	F173	AM J PHYSIOL
STERKERS O	1987	253	F50	AM J PHYSIOL
WALLACE D C	1992	256	628	SCIENCE
WOOLLINS J D	1983	2	175	POLYHEDRON
YAMASOBA T	1998	784	82	BRAIN RES
YAMASOBA T	1999	815	317	BRAIN RES

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STRUCTURE FILE UPDATES:   15 JUL 2004  HIGHEST RN 710826-40-7
DICTIONARY FILE UPDATES:  15 JUL 2004  HIGHEST RN 710826-40-7

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=> s  59-51-8 or  1982-67-8 or  58569-55-4 or  5072-26-4 or 63-68-3 or 7005-18-7

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             1 58569-55-4
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             1 5072-26-4
               (5072-26-4/RN)
             1 63-68-3
               (63-68-3/RN)
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               (7005-18-7/RN)
L78          5 59-51-8 OR  1982-67-8 OR  58569-55-4 OR  5072-26-4 OR 63-68-3
               OR 7005-18-7

=> d ide 1-5; fil hom

L78  ANSWER 1 OF 5  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   58569-55-4  REGISTRY
CN   1-5-Adrenorphin (human) (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Adrenorphin (human), 6-de-L-arginine-7-de-L-arginine-8-de-L-valinamide-
OTHER NAMES:
CN   .beta.-Endorphin(1-5)
CN   105: PN: US20030119021 SEQID: 92 unclaimed sequence
CN   12: PN: US6258556 SEQID: 12 unclaimed sequence
CN   153: PN: US20030176421 PAGE: 54-55 claimed protein
CN   18: PN: US6284459 SEQID: 33 unclaimed sequence
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CN   210: PN: WO0069900 SEQID: 882 unclaimed sequence
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CN   34: PN: US6319668 SEQID: 33 unclaimed sequence
CN   46: PN: US6017496 PAGE: 120 claimed protein
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CN 4: PN: US6395513 SEQID: 7 unclaimed sequence
CN 5-L-Methionine-enkephalin
CN 5-Methionine enkephalin
CN 6: PN: WO0130371 TABLE: 1 unclaimed sequence
CN 7: PN: WO0130371 TABLE: 1 unclaimed sequence
CN 9: PN: WO03061683 FIGURE: 1 unclaimed sequence
CN 9: PN: WO2004041151 SEQID: 9 unclaimed sequence
CN Enkephalin, methionine
CN Human .beta.-endorphin(1-5)
CN L-Methionine, L-tyrosylglycylglycyl-L-phenylalanyl-
CN L-Methionine-enkephalin
CN Lupex
CN Met-enkephalin
CN Met5-enkephalin
CN Methionine enkephalin
CN Methionyl-enkephalin
CN NSC 374896
CN Opioid growth factor
CN Peptid-M
CN PN: US5961923 PAGE: 135 claimed protein
CN Porcine .beta.-endorphin 1-5
CN Tyr-Gly-Gly-Phe-Met-OH
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C27 H35 N5 O7 S
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LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, NAPRALERT, PHAR, PROMT, PROUSDDR, RTECS*, SPECINFO, TOXCENTER, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Conference; Dissertation; Journal; Patent; Preprint; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
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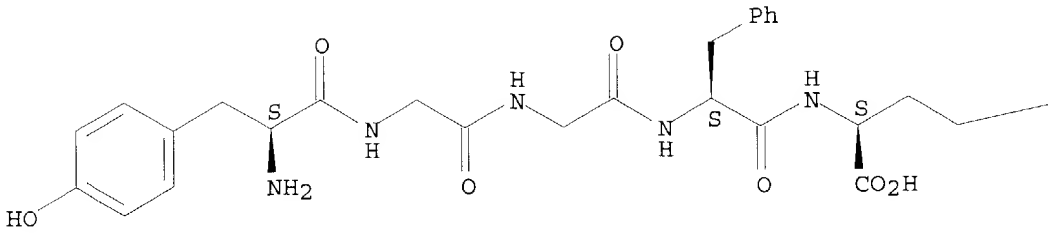
RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

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93 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
5572 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L78 ANSWER 2 OF 5 REGISTRY COPYRIGHT 2004 ACS on STN
RN **5072-26-4** REGISTRY
CN Butanoic acid, 2-amino-4-(S-butylsulfonimidoyl)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Sulfoximine, 3-amino-3-carboxypropyl butyl (6CI)
CN Sulfoximine, S-(3-amino-3-carboxypropyl)-S-butyl- (7CI, 8CI)
OTHER NAMES:
CN Buthionine sulfoximine
CN Butionine sulfoximine
CN DL-Buthionine (S,R)-sulfoximine
CN NSC 381100
FS 3D CONCORD
DR 71765-30-5
MF C8 H18 N2 O3 S
LC STN Files: ADISINSIGHT, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CIN, CSCHEM, CSNB, DDFU, DRUGU, EMBASE, IMSRESEARCH, IPA, MEDLINE, MRCK*, NIOSHTIC, PROMT, PROUSDDR, RTECS*, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
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RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
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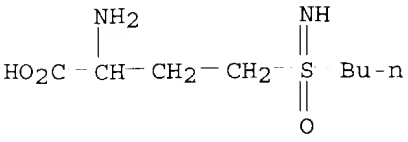

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7 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
555 REFERENCES IN FILE CAPLUS (1907 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L78 ANSWER 3 OF 5 REGISTRY COPYRIGHT 2004 ACS on STN
RN **1982-67-8** REGISTRY
CN Butanoic acid, 2-amino-4-(S-methylsulfonimidoyl)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Sulfoximine, S-(3-amino-3-carboxypropyl)-S-methyl-, DL- (6CI, 8CI)
OTHER NAMES:
CN DL-Methionine-DL-sulfoximine
CN Methionine sulfoximine
FS 3D CONCORD
DR 407-40-9, 63038-25-5, 2676-35-9
MF C5 H12 N2 O3 S
CI COM
LC STN Files: AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, NAPRALERT, NIOSHTIC, RTECS*, TOXCENTER, USPATFULL, VETU
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Other Sources: EINECS**
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DT.CA CAplus document type: Conference; Dissertation; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)
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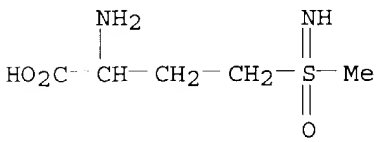

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528 REFERENCES IN FILE CAPLUS (1907 TO DATE)
26 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L78 ANSWER 4 OF 5 REGISTRY COPYRIGHT 2004 ACS on STN
RN **63-68-3** REGISTRY
CN L-Methionine (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Methionine, L- (8CI)
OTHER NAMES:
CN (S)-2-Amino-4-(methylthio)butanoic acid
CN .alpha.-Amino-.gamma.-methylmercaptobutyric acid
CN .gamma.-Methylthio-.alpha.-aminobutyric acid
CN 1139: PN: WO2004048938 SEQID: 1139 claimed protein
CN 2-Amino-4-(methylthio)butyric acid
CN 395: PN: US20030049618 SEQID: 395 claimed protein
CN Acimethin
CN Butanoic acid, 2-amino-4-(methylthio)-, (S)-
CN Cymethion
CN h-Met-oh
CN L-(-)-Methionine
CN L-.alpha.-Amino-.gamma.-methylthiobutyric acid
CN L-Homocysteine, S-methyl-
CN l-Methionine
CN Methionine
CN NSC 22946
CN Protein (human clone US2003/0049618-SEQID-395 secreted protein sequence homolog)
CN S-Methionine
CN Soft tissue sarcoma-associated protein (human clone WO2004048938-SEQID-1139)
FS STEREOSEARCH
DR **7005-18-7, 24425-78-3**
MF C5 H11 N O2 S
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LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DRUGU, EMBASE, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PIRA, PROMT, PS, RTECS*, SPECINFO, TOXCENTER, TULSA, ULIDAT, USAN, USPAT2, USPATFULL, VETU, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Book; Conference; Dissertation; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
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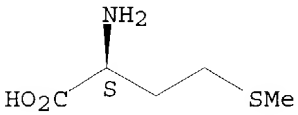
RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

Absolute stereochemistry.



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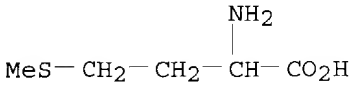
34907 REFERENCES IN FILE CAPLUS (1907 TO DATE)
10 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L78 ANSWER 5 OF 5 REGISTRY COPYRIGHT 2004 ACS on STN
RN **59-51-8** REGISTRY
CN Methionine (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN DL-Methionine
CN Methionine, DL- (8CI)
OTHER NAMES:
CN (.+-.)-Methionine
CN .alpha.-Amino-.gamma.-methylmercaptobutyric acid
CN Acimetion
CN Amurex
CN Banthionine
CN Cynaron
CN DL-2-Amino-4-(methylthio)butyric acid
CN Dyprin
CN Lactet
CN Lobamine
CN Meonine
CN Meprom M 85
CN Methilanin
CN Metione
CN Neston
CN NSC 9241
CN Pedameth
CN Racemethionine
CN Urimeth
FS 3D CONCORD
MF C5 H11 N O2 S
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DETHERM*, DIOGENES, EMBASE, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PIRA, PROMT, RTECS*, TOXCENTER, TULSA, ULIDAT, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Conference; Dissertation; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)

RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3011 REFERENCES IN FILE CA (1907 TO DATE)
64 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3013 REFERENCES IN FILE CAPLUS (1907 TO DATE)
3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

FILE 'HOME' ENTERED AT 16:50:07 ON 16 JUL 2004